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BEFORE THE BOARD OF PATENT APPEALS

AND INTERFERENCES

Ex Parte MARK S. CHEE and JOHN R. STUELPNAGEL

Appeal 2009-000287
Application 09/513,362
Technology Center 1600

Oral Hearing Held: May 20, 2009

Before CAROL A. SPIEGEL, ROMULO H. DELMENDO, and RICHARD M. LEBOVITZ, *Administrative Patent Judges.*

APPEARANCES:

ON BEHALF OF THE APPELLANT:

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PROCEEDINGS

MS. BOBO-ALLEN: Good afternoon. Calendar No. 49, Appeal No. 2009-0287, Ms. Spain.

MS. SPAIN: Thank you.

JUDGE SPIEGEL: Good afternoon. We are here for Appeal No. 2009-000287, *Ex Parte* Mark S. Chee, serial no. 09/513,362. We'd like to welcome counsel and our guests. If they would please introduce themselves, and then, counsel, you will have 30 minutes to present your arguments.

MS. SPAIN: Thank you.

MR. MURPHY: Hi. I am John Murphy --

JUDGE SPIEGEL: Welcome.

MR. MCCARTHY: Wayne McCarthy. I work for 454 Life Sciences.

JUDGE SPIEGEL: Welcome. Oh, just one other point of order. If you have cell phones with you, would you please put them on vibrate or turn them off, please? Thank you.

COURT REPORTER: I hate to interrupt, but if it's okay, I guess at the end of the hearing if you could submit a business card to me with your name on it?

MS. SPAIN: I will do that. Please remind me if I forget.

COURT REPORTER: Okay.

MS. SPAIN: Thank you very much. We are appealing this obviousness rejection because we believe that it has two fundamental flaws associated with it. First, it is our opinion that the Examiner has not articulated with sufficient reason and explicit analysis a *prima facie* case for combining the specific nuclear sequencing method of Rothberg et al. with

the bead system of Walt et al. Secondly, we believe that the Rothberg et al. reference includes an express teaching away from modifying a pyrosequencing system by introducing beads into it. And we further believe that the record of the continuation-in-part application corroborates and confirms what we believe is an express teaching away in the Rothberg et al. patent.

I want to briefly step through the main steps of the -- at least most of the independent claims and of the key method steps. Our method, as you know, is directed at sequencing a plurality of target nucleic acids. Our method provides an array that contains discrete sites on a substrate. Each discrete site contains a microsphere and also contains an enzyme. Our method provides for two subpopulations of beads that, in a later step, form hybridization complexes, the first and second primers, that are then used to extend the target nucleic acids that are attached to the beads by adding nucleotides. The nucleotides have a pyrophosphate attached to them, so that if there is a match between the target nucleic acid and the added nucleotide, the pyrophosphate is released and the attached enzyme in the discrete site then converts the pyrophosphate that is released into the detectable signal. And these method steps are used to determine the sequence of the target nucleic acid. The rejection in this case centers on one issue, and that is, is there a reason –- yes?

JUDGE SPIEGEL: If you, please. In your Claim 1, step B, you refer to a first domain of a first target sequence.

MS. SPAIN: In step -- in --

JUDGE SPIEGEL: Claim 1, step B.

MS. SPAIN: Step B. Oh, yes.

JUDGE SPIEGEL: And in step C, you talk about a second domain of a second target sequence. Are we talking about two different target nucleic acids here?

MS. SPAIN: Not necessarily. So the way to visualize this is that the target domains can be overlapping, there can be different target domains on different DNA molecules. So the way it works is -- the way that we framed the target domain issue really is to capture the idea that in a later step we form the hybridization complexes with distinct primers that recognize distinct sequences. In order to make that flow, we arbitrarily say that nucleic acids have different domains.

JUDGE SPIEGEL: Well, the confusion was because the preamble of the claim said that -- the target positions, is that supposed to be target sequences?

MS. SPAIN: Yes. Those are the positions that are sequenced, and it could have -- the claim could have said that both the first domain and the second domain contain the target positions. We didn't spell it out that way.

JUDGE SPIEGEL: Okay. Thank you.

MS. SPAIN: Thank you. The central issue in this rejection is, as you know, it's an obviousness rejection, and the question is, is there a reason -- would one skilled in the art have a reason to combine or modify the pyrosequencing methods of Rothberg et al. by introducing the beads of Walt et al. into that system? As a first issue, it is our opinion that the Examiner has not articulated with sufficient specificity a prima facie case, and the reasons for that are as follows. When you look at the record, which I know

you have, you see that when the Examiner describes -- the Examiner frames the argument in terms of motivation, as you know. That's not necessarily the argument it has to be, but she frames it in terms of motivation. You can frame it in terms of is there a reason to combine the references. In any event, the Examiner quotes verbatim. She quotes two sections out of the *World Patent* and reproduces it, and says "Here is the motivation to combine." Several times on the record we have requested that the Examiner please clarify how that motivation to combine fits into the pyrosequencing, which is an element of our claim.

JUDGE LEBOVITZ: Well, to interrupt, doesn't Walt tell you that you can use its microbead arrays for detecting nucleic acids, including detecting sequences, mutations? It does, doesn't it?

MS. SPAIN: Yes.

JUDGE LEBOVITZ: So, isn't sequencing just a routine way of detecting mutations?

MS. SPAIN: The Walt patent is really not aimed at, as you know, sequencing, as much as it is aimed at synthesis. And when you look at the specific quoted excerpts that are cited, you will see that they are in the context of nucleic acid synthesis.

JUDGE LEBOVITZ: Right.

MS. SPAIN: And the reason this is a significant issue is because synthesis and sequencing have different aspects and different technical considerations underlying them. One example, if I may, is -- a big point that is made in those sections that are quoted to provide motivation, is the whole issue of the ability to code and decode. Where -- the Examiner cites this

also in her answer -- where the issue is that one of the benefits here is that you can -- you can do a lot of the synthesis apart from the array, you can code it, then load it randomly on the array, and then later on, you can decode. That is really not applicable to a method where you're trying to sequence nucleic acids because you wouldn't know what to code a priori. Your decoding is the sequencing step. So the whole coding and decoding advantage is of limited usefulness in a system of synthesis.

JUDGE LEBOVITZ: Yes, but we don't want to necessarily get caught in misstatements or characterizations made by the Examiner, and I don't know whether the Examiner was correct or not. The real issues here are whether the references suggest the claims method, and if you have Walt telling you repeatedly throughout it that you can use it to detect nucleic acids, that you can use it to detect mutations in nucleic acids, and sequencing is one way of detecting mutations, then why wouldn't it be obvious to put those two together, aside from, you know, the examiners, sometimes they go off in different directions, but we have to focus on what the references teach, not on sort of isolated statements that the Examiner made.

MS. SPAIN: Your Honor, let me address that. And I agree with you, and my purpose here is not picking on the Examiner. In fact, I think this is a very -- she is a great Examiner. I have worked with her on a lot of cases. She is extremely bright and we enjoy working with her; the client enjoys working with her. That is not the point. Our disagreement on the prima facie case is, regardless of trying to trip somebody over misstatements, the burden is on the Examiner to articulate with specificity why Walt can be combined, why Rothberg can be modified. This is the burden the law, as

you know, places upon the Examiner. And when the Examiner doesn't meet that burden, then, she falls short of establishing a prima facie case. And I am happy to address the substantive issues in a second. But let me please read from the Answer, where the Examiner states that, after we asked of her, the statements of Walt are rather --

JUDGE SPIEGEL: Excuse me. Page?

MS. SPAIN: Oh, sorry. The Examiner's Answer, page 18.

JUDGE SPIEGEL: Thank you.

MS. SPAIN: As the statements of Walt are rather self-explanatory, one of ordinary skill in the art would not need any further explanatory comments added to understand the benefits offered by the bead system. Walt doesn't mention, expressly or implicitly, pyrosequencing. Walt doesn't, doesn't talk about pyrosequencing. The Examiner never utters the term pyrosequencing when she talks about combining the references. I think, with all due respect, this falls short of the burden that is placed to articulate why the specific method of pyrosequencing, which is -- and we will be going to the substance of it in a second, which actually is a method that has some intricacies to it. For example, the necessity to perform a washing step after each nucleotide addition, which poses particular technical issues; the issue of lateral diffusion, because of the pyrophosphate. I think these types of issues that make pyrophosphate sequencing unique, technically, need to be addressed in a prima facie case because they bear upon the prima facie case and upon the reason the skilled person would have to combine or not combine the two references.

So moving from the procedural issue, important but procedural issue, of the prima facie case to the issue of why one would not be -- and that was, Judge Lebovitz, your question was let's look at the substance here. Why wouldn't you -- Walt says, you know, you can detect. Why wouldn't you throw it into the pryosequencing method of Rothberg? And the answer to that question, it is our position that the skilled person, for a number of reasons, would be disinclined to do so. One of those reasons is, and I already mentioned it, that some of the advantages that Walt talks about, such as the coding and decoding, as well as others, do not translate, in terms of the advantage, into our method because they relate to synthesis, not sequencing. So looking at those benefits, you would appreciate them, but say that is not for me, a motivator, to put these in this system.

JUDGE LEBOVITZ: The only problem with that statement is in -- and it may be a side, but I am just going to point out -- that sequencing is synthesis. Pyrosequencing is synthesis, right? That's what you're doing. Aren't you incorporating nucleotides?

MS. SPAIN: It is an incorporation of nucleotides, along the target nucleic acid, however, it is not a situation whereas -- and a lot of -- where you have a situation where -- Walt says one of our great advantages is that we can do part of -- perform part of the synthesis *a priori*, and then put a code on it, and then throw it onto the array. We can't do that for sequencing. We don't know what the sequence is. So such other -- there are plenty -- there are other advantages that Walt talks that might be applicable, at least in part, to our invention, and I am not going to tell you there are not.

However, my point is that the disadvantages outweigh these advantages. For example, one of the big issues in pyrosequencing is -- there are two big issues. One is the bead loss, and we can get to that when we talk about the teaching of Walt, but another one is the issue of lateral diffusion. And one thing that is critical to preventing the lateral diffusion issue is to have good spacing, so that the signals don't run into each other. This is easily conceptualized.

Anytime you put beads in a system like this, you displace volume. You displace volume that is normally there for the diffusion process. And that is one reason why one skilled in the art, I urge you, would look at the Walt reference and say, "You know, if I put those beads into this pyrosequencing system, that might not be good for me because I have to deal with lateral diffusion." And then they might look at the Rothberg reference itself and say, "Rothberg knew about these. Rothberg, in column 20, cites the *World*. Michael, et al. It's the *World* group. They talk about the fiber etching. They talk about the wells. That reference includes beads. Rothberg is well aware of that reference. Rothberg talks about beads. Rothberg, at column 21, starting at line 9, talks about optimizing the pyrosequencing process, and they talk about the early days of pyrosequencing, and they cite to a 1996 reference by Ronaghi et al. and they say, "Wow, in these early studies, they use beads." And then they go on and say -- and I am going to quote so I am not overreaching, or underreaching for that matter. "However, it was found that the loss of beads during washing, which was performed between each nucleotide and enzyme addition, was the limiting factor to sequence longer stretches." So here, they

conclude that this was a limiting factor. And then they never mention beads again. They are aware of beads. They are aware of Michael et al.'s work. They are extraordinarily skilled in the art. They don't touch beads again. Instead, they have a great alternative: attach the reactants directly to the substrate. That way, you don't displace volume, and, at the same time, you maximize your lateral diffusion mitigation, and at the same time, you don't have to deal with the bead loss and the sample loss of Ronaghi. Never mentioned beads again. They move on.

Then, in the continuation-in-part application -- and I want to be very straightforward here. We are citing the statements in the continuation-in-part application for a very limited purpose, and the purpose is simply to say that we're not the only ones who look at this statement and say this is a teaching away from using beads in pyrosequencing, the bead loss issue.

Later on, the Inventors, on the record, as well as Declarants, and in an acknowledgment actually in the note -- in the reasons for allowance by the Examiner, state that the bead loss issue was an expressed problem. In fact, the Declarant, Margulies, in a Declaration filed in April of 2004, that we submitted as an exhibit in this case, states that, let me quote again, "The application," and this is our primary reference here, "expressly recognizes the problem of bead sample loss during the sequencing reaction." So, here, what he is saying is yes, he agrees with what we're saying. On its face, this is a teaching away from the combination of pyrosequencing and the Walt beads. Furthermore, when you look at the Ronaghi reference that is of record here, as indicated in the Examiner's answer, where she lists the references of record -- it has also been discussed -- it is mentioned in the

Examiner's Answer at page 20, where he says that the answer is easy, you just fix the beads. Well, the only person who is talking about fixing beads is Walt and I have already discussed why Walt's beads are not useful in our method. But when we look here at Ronaghi, and we look at the actual quote from Ronaghi, it says, "For example -- for instance --" I apologize, "by immobilization of the DNA template in a capillary, the template loss observed so the pair of magnetic beads could be avoided. Ronaghi isn't talking about putting DNA on beads and fixing the beads. Ronaghi is suggesting the exact same thing Rothberg did. Put it directly to the substrate. Fix it.

JUDGE LEBOVITZ: But didn't Walt solve the problem of putting microspheres on a substrate and using that to simultaneously multiplex a lot of chemical reactions? So, even if there were statements in Rothberg that led one to believe that there might be problems with beads, it seems that that problem was addressed by Walt.

MS. SPAIN: I would respectfully submit that for the reasons we just discussed, that problem was not addressed in Walt. Walt wasn't able to address that problem because Walt wasn't addressing our claim element or Rothberg's pyrosequencing method. So, therefore -- and again, this goes back to the leg of a prima facie case and something you really -- in order for this obviousness rejection to stand, and for this -- and I believe it can't, because it doesn't have the legs to stand -- is that there needs to be -- Walt talks about advantages in general of using beads for multiplexing, for separating the synthesis from the assay, for being able to quickly change out things, for being able to do things randomly and then decode them. The

problem is, some of these references -- some of these advantages -- several of these advantages, as I have lined out, do not apply to --wouldn't provide an advantage to us performing our method, for reasons I have already explained, and, secondly, we're talking about displacing volume here. And displacing volume is not an issue, and is outweighed by Walt's advantages in multiplexing and a lot of things, until you put it into a pyrosequencing reaction. And that is where the claims are, and that is the case that has to be made for obviousness. The elements of the claim matter.

JUDGE LEBOVITZ: So, your argument is Walt teaches what it may teach about using microspheres and arrays, but if you're thinking about applying that technology to pyrosequencing, you'd look at the Rothberg reference, and the Rothberg reference would tell you why you wouldn't do what Walt said for pyrosequencing?

MS. SPAIN: That is exactly the argument, with some additions, but that is the argument.

JUDGE LEBOVITZ: Right.

MS. SPAIN: And I mean Ronaghi supports it. The two references on this record that deal with pyrosequencing say no beads. No beads. But if you want to prevent the bead loss, you attach it directly to the substrate.

JUDGE LEBOVITZ: The Ronaghi reference.

MS. SPAIN: Yes. And that is on page -- in case -- that is at page 88 of Ronaghi. And, with all due respect, it wasn't cited in the Examiner's Answer because she said the problem -- the solution that is proposed here is just as Walt fixed beads to capillaries and immobilized them, but the sentence, when you read it, actually suggests exactly what Rothberg says,

"Fix the DNA template directly to a capillary and take the beads out of the equation." And there is a reason for that.

JUDGE SPIEGEL: Well, thank you very much, Ms. Spain, and we will take the case under advisement.

MS. SPAIN: Thank you very much for your time.

COURT REPORTER: Thank you. Before you go, I just need to get a couple of spellings from you. Ronaghi, how is that spelled?

JUDGE SPIEGEL: R-O-N-A-G-H-I.

COURT REPORTER: Okay, H-I?

JUDGE SPIEGEL: Exactly.

COURT REPORTER: And Rothberg?

JUDGE SPIEGEL: R-O-T-H-B-E-R-G.

COURT REPORTER: Okay. And was it Walt? Was that it?

MS. SPAIN: Walt, W-A-L-T.

JUDGE SPIEGEL: Right, like Walt Disney.

COURT REPORTER: Yes, that's what I thought. I just wanted to make sure, though. And this other one you referenced here, I think it was beads?

MS. SPAIN: Beads, B-E-A-D-S.

COURT REPORTER: Okay.

JUDGE LEBOVITZ: What about pyrosequencing?

COURT REPORTER: Yeah, that's the other one.

JUDGE SPIEGEL: P-Y-R-O --

COURT REPORTER: P-Y-R-O --

JUDGE SPIEGEL: Sequencing.

COURT REPORTER: Okay.

JUDGE LEBOVITZ: Like Fahrenheit 454.

COURT REPORTER: All right. Thank you very much.

JUDGE SPIEGEL: We're off the record.

(Whereupon, the hearing concluded on May 20, 2009.)

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C E R T I F I C A T E

This is to certify that the attached proceedings before the U.S. Patent and Trademark Office in the matter of:

Ex Parte MARK S. CHEE, et al.

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